Changing Cigarette Habits and Bladder Cancer Risk: A Case-Control Study [1]

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ABSTRACT—With the use of data from the 8,764 subjects in the National Bladder Cancer Study, the separate contribution of various aspects of a person's cigarette smoking history to his increased risk of bladder cancer was estimated. These estimates have not been previously available, owing to the smaller sizes of earlier studies. Our data indicated that people who have only smoked unfiltered cigarettes have higher risks than those who have only smoked filtered cigarettes but that people who have switched from unfiltered to filtered have experienced no reduction in risk. Our data also indicated that smoking cessation substantially reduced the risk. The former smoker appeared to benefit both because he stopped adding to the burden of irreversible damage and because he ceased being exposed to some reversible hazard. Thus the former smoker had a lower risk than the current smoker even though they had smoked the same number of cigarettes daily for the same number of years, but the former smoker's risk remained higher than the risk of a person who never smoked. Our data suggest that one-half of the bladder cancer occurring among men in the United States and one-third of that among women is caused by cigarette smoking.—JNCI 1987; 78:1119–1125.

Cigarette smoking was linked to bladder cancer in 1956 (*1*), and numerous subsequent studies have confirmed the association (*2–10*), but the effects of changes in smoking habits on bladder cancer risk have not been clearly demonstrated. In particular, the effects on bladder cancer risks of quitting smoking or of switching from unfiltered to filtered cigarettes have not been established. In part, this is because very large studies are needed to disentangle the effects of highly correlated smoking variables. In addition, the magnitude of the smoking-associated risks and the long latent period make it more difficult to assess separate smoking effects on bladder cancer risk than on lung cancer risk, for example. Using data from the largest case-control interview study of bladder cancer to date, we have estimated the RRs of bladder cancer according to changes in cigarette smoking habits.

METHODS

Data collection.—We interviewed 2,982 cases and 5,782 controls as part of the National Bladder Cancer Study, a collaborative, population-based, case-control study conducted in 10 geographic areas of the United States. The case group was composed of all identified residents of the areas aged 21–84 who were diagnosed with histologically confirmed bladder cancer in a 1-year period (with the beginning time varying among areas from December 1977 to March 1978). Cases were identified from cancer registries, nine of which were part of the National Cancer Institute Surveillance, Epidemiology, and End Results Program. The control group was randomly selected from the general population (weighted by the age, sex, and geographic distribution of the cases). Controls aged 21–64 were selected from 22,633 households chosen by telephone sampling with the use of random-digit dialing. Controls aged 65–84 were selected from Health Care Financing Administration rosters. Details of the study methods are presented elsewhere (*11*).

We identified 4,086 cases and interviewed 2,982 (73%) of them. The remaining 1,104 were not interviewed because of death (282), illness (288), patient refusal (252), physician refusal (128), being identified after the study ended (65), not being found (81), and other reasons (8). A total of 4,057 controls older than 64 were identified, of whom 3,313 (82%) were interviewed. The remaining 744 were not interviewed because of death (94), illness (174), refusal (348), not being found (105), and other reasons (23). From telephone sampling of households, 2,928 peo-

ABBREVIATIONS USED: CI=confidence interval; RR=relative risk.

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ple younger than 65 were selected as controls, of whom 2,469 (84%) were interviewed. The remaining 459 were not interviewed because of death (7), illness (23), refusal (335), not being found (87), and other reasons (7).

All subjects were interviewed at home. They were asked about their smoking habits in detail including the dates when they started or stopped smoking for 6 months or more, the usual and maximum amounts smoked, and their usual depth of inhalation. Data were collected separately for filtered and unfiltered cigarettes. Data on other forms of tobacco use were also recorded, the findings from which have been reported (12).

Analysis.—The effects of smoking habits on bladder cancer risk were estimated by the observed RR. Maximum likelihood estimates were derived from multiple logistic regression models with terms entered for the exposures and for potentially confounding variables (13). In each analysis presented, we examined the possibility of confounding by age (in six categories), sex, area of residence, race, and exposure to high-risk occupations. High-risk occupations were those suspected to be hazardous on the basis of existing data and those estimated in these data to have an RR of 1.5 or more.

In some of the analyses presented, comparisons can only be made within the group of subjects who have smoked, because of the need to adjust for smoking variables. The reference or "unexposed" category in such analyses is indicated in the table or text. For continuous variables that were categorized in the tables, we computed tests for trend by assigning consecutive integer scores and by fitting a logistic regression model. We estimated etiologic fractions following the method of Cole and MacMahon (14).

Time-related variables.—Examination of the temporal aspects of cigarette smoking was constrained by the fact that the variables of interest are a linear combination for most smokers (age at diagnosis = age at starting + duration + time since quitting). In our data, 83% of smokers (4,415/5,301) were in this group. The remaining smaller proportion of smokers had quit smoking and resumed at least once. Within the latter group, the temporal variables are not perfectly correlated unless length of nonsmoking interlude is added to the list. Therefore, in the larger group of smokers, it is impossible to examine the effect of age at diagnosis, age at starting, duration, or times since quitting while controlling for the other three factors. It is possible to control for two factors and to estimate the effect attributable to the remaining two. In the smaller group of intermittent smokers, it is possible to control for age at diagnosis, age at starting, and duration and to attribute the remaining effect to time since quitting or length of nonsmoking interlude.

TABLE 1.—*Estimated bladder cancer RR, according to various measures of cigarette exposure, compared to nonsmokers*

Category	No. of cases	No. of controls	Estimated RR[a]	95% CI
Never smoked	657	2,198	1.0	
Ever smoked	2,324	3,581	2.3	2.0-2.5
Current smoker	1,151	1,416	2.9	2.6-3.3
Former smoker	927	1,841	1.7	1.5-2.0
Time since stopped, yr[b]				
≥40	67	139	1.5	1.1-2.1
30-39	75	196	1.3	1.0-1.7
20-29	174	347	1.7	1.4-2.1
10-19	277	606	1.6	1.4-1.9
1-9	334	553	2.2	1.9-2.6
Duration, yr[b]				
<20	272	681	1.4	1.2-1.6
20-39	800	1,317	2.1	1.9-2.4
40-59	896	1,130	2.8	2.5-3.2
≥60	110	129	3.2	2.4-4.2
Average dose rate, No./day[b]				
<20	568	1,125	1.8	1.6-2.0
20-39	1,102	1,547	2.6	2.3-2.9
≥40	392	556	2.6	2.2-3.0
Total dose, pack-yr[b]				
1-19	383	941	1.5	1.2-1.7
20-39	532	871	2.2	1.9-2.5
40-59	564	751	2.7	2.4-3.2
60-79	291	305	3.5	2.9-4.2
80-99	131	196	2.4	1.9-3.1
≥100	161	164	3.7	2.9-4.7
Age started, yr[b]				
≥30	144	330	1.5	1.2-1.8
25-29	110	228	1.6	1.3-2.1
20-24	398	691	2.1	1.8-2.4
15-19	988	1,410	2.6	2.3-2.9
5-14	435	593	2.8	2.4-3.2

[a] Estimates are adjusted for age, sex, and race and are relative to subjects who never smoked.
[b] *P*-value of test for trend was <.001.

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RESULTS

The number of years since cessation, the number of years of smoking, the average daily number of cigarettes, the total lifetime number of cigarettes, and the age at starting to smoke were all related to risk, after adjustment for the effects of sex, race, and age (table 1). As shown in table 1, subjects smoking during the year before interview (current smokers) faced an estimated risk of bladder cancer about three times as high as the risk to subjects who never smoked cigarettes. Former smokers had an intermediate risk. Even after adjustment for the number of years of cigarette smoking (duration), the average number of cigarettes smoked daily (dose rate), depth of inhalation, and whether filtered cigarettes were smoked (filtration), current smokers still showed a 50% higher risk than former smokers (estimated RR=1.5, 95% CI=1.3-1.7).

The variables shown in table 1 were related to each other. For example, the study subjects of a given age with the longest duration of exposure also tend to be those with the shortest time since stopping. In addition, the total dose (measured in pack-yr) is merely the product of duration and dose rate. In table 1, the RRs are estimated by using the bladder cancer risk among subjects who never smoked as the baseline, and the effects of the smoking characteristics are not adjusted for each other. Subsequent analyses separate the effects of the interrelated variables.

As shown in table 2, duration was a strong independent predictor of age-adjusted risk and dose rate and whether smoking currently exerted additional effects. At every level of duration and dose rate, current smokers had higher RRs than former smokers. The effect of duration was more pronounced among former than current smokers. Conversely, the effect of dose rate was more pronounced among current smokers. When duration and dose rate were treated as continuous variables in a regression model (including a term for filtration) fitted to the data from current smokers, the estimated increase in bladder cancer risk was 0.9% for each additional year of smoking ($P=.073$) and 1.4% for each additional cigarette smoked daily ($P<.001$). The corresponding estimates for former smokers were 1.4% for each additional year ($P=.000$) and 0.3% for each additional cigarette ($P=.224$). The former and current smokers had statistically significantly different dose rate effects ($P=.002$) and different duration effects ($P=.009$). These point estimates varied slightly depending on the precise logistic model chosen, but in all of the models we fitted the effect of duration was stronger among former smokers; the effect of dose rate was stronger among current smokers. Subjects who had smoked heavily for 20 years and who were still smoking during the year before the study faced a bladder cancer risk four times as high as the risk faced by subjects who never smoked.

Table 3 compares people who quit smoking or who switched to filtered cigarettes or both to those who continued to smoke nonfiltered cigarettes. The beneficial effect of quitting is again apparent. Filtration shows a paradoxical effect, with the lowest risk occurring among people who only smoked filtered cigarettes but the highest risk occurring among those who switched from unfiltered to filtered cigarettes. These relationships are further examined in tables 4-6.

TABLE 2.—*Estimated RR of bladder cancer, according to duration, dose rate, and whether smoking currently*

Category	Duration[a]		
	<20 yr	20-39 yr	≥40 yr
Former smokers			
<20/day	1.3 (1.1-1.7)	1.5 (1.2-1.9)	1.9 (1.4-2.6)
20-39/day	1.4 (1.1-1.9)	1.8 (1.5-2.2)	2.5 (2.0-3.2)
≥40/day	1.0 (0.6-1.5)	2.1 (1.6-2.7)	2.8 (2.0-3.8)
Current smokers			
<20/day	1.7 (1.0-2.7)	1.6 (1.2-2.2)	2.7 (2.2-3.3)
20-39/day	2.2 (1.3-3.7)	3.8 (3.0-4.6)	3.1 (2.6-3.6)
≥40/day	2.4 (1.1-5.4)	4.0 (2.7-5.9)	3.8 (2.8-5.0)

[a] Estimates are adjusted for age, sex, and race. Risk is relative to 657 cases and 2,198 controls who never smoked. 95% CIs are shown *in parentheses.*

Cessation

Table 4 presents in detail estimates of effect of time since quitting, with the data presented separately for continuous smokers (those who did not quit and resume) and for intermittent smokers because they offer different possibilities for adjusting for the effects of the correlated time-related variables. Among the 4,415 continuous smokers, those who had stopped smoking 10 years before the study began enjoyed a 40% reduction in risk compared to current smokers (estimated RR=.6). Not all of this reduction in risk was attributable to a lower total duration of exposure since the reduction in risk was still 10-30% after duration was taken into account (estimated RR=.7-.9). This residual effect of more time since quitting cannot be distinguished from the effect of earlier age at starting.

Age at starting can be controlled among the 886 intermittent smokers, and the resulting estimates show a steeper decline in risk, with smokers who had quit at least 10 years before diagnosis showing an RR of 0.4-0.5 compared to current smokers. The data also show a marked decline in RR within 2-4 years of stopping. Although the estimates among intermittent smokers can be controlled for age at diagnosis, duration, and age at starting, they cannot be controlled additionally for the length of nonsmoking intervals accrued between episodes of smoking. Thus the reduction in risk could be the effect of shorter nonsmoking intervals between episodes of smoking, but such an effect is not very plausible.

In total, subjects who had stopped smoking 10 years

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TABLE 3.—*Estimated RR of bladder cancer according to change in smoking habits*

Category	No. of cases	No. of controls	Estimated RR[a]	95% CI
All ages, 21-84 yr				
Still smoking				
Nonfiltered only	253	320	1.0	—
Switched <15 yr ago	99	83	1.5	1.0-2.1
Switched ≥15 yr ago	651	739	1.1	0.9-1.4
Filtered only	98	216	0.6	0.4-0.8
Quit smoking <10 yr ago				
Nonfiltered only	118	180	0.8	0.6-1.1
Switched to filtered	177	289	0.8	0.6-1.0
Filtered only	26	53	0.6	0.4-1.1
Quit smoking ≥10 yr ago				
Nonfiltered only	430	917	0.6	0.5-0.7
Switched to filtered	113	238	0.6	0.5-0.8
Filtered only	19	58	0.4	0.2-0.7
Ages 21-64 yr				
Still smoking				
Nonfiltered only	134	149	1.0	
Switched <15 yr ago	56	47	1.3	0.8-2.0
Switched ≥15 yr ago	386	430	1.0	0.8-1.3
Filtered only	65	147	0.5	0.3-0.7
Quit smoking <10 yr ago				
Nonfiltered only	36	77	0.5	0.3-0.8
Switched to filtered	73	148	0.5	0.4-0.8
Filtered only	12	40	0.4	0.2-0.7
Quit smoking ≥10 yr ago				
Nonfiltered only	102	260	0.5	0.3-0.6
Switched to filtered	45	109	0.5	0.3-0.7
Filtered only	9	31	0.3	0.2-0.7

[a] Estimates are adjusted for age, sex, race, and dose rate.

TABLE 4.—*Estimated RR of bladder cancer according to time since quitting smoking*

Years since quitting	No. of cases	No. of controls	Estimated RR adjusted for:		
			Age, sex, and race	Age, sex, race, and duration	Age, sex, race, duration, and starting
Continuous smokers					
0, current	883	1,110	1.0	1.0	
1	50	65	1.0	1.0	
2-4	85	168	0.6	0.7	
5-9	150	219	0.9	0.9	
10-19	243	511	0.6	0.7	
≥20	295	636	0.6	0.9	
Trend, *P*-value			<.001	.02	
Nonsmokers			0.4		
Intermittent smokers[a]					
0	268	306	1.0	1.0	1.0
1	14	24	0.7	0.7	0.7
2-4	16	34	0.5	0.5	0.5
5-9	19	43	0.5	0.5	0.4
10-19	34	95	0.4	0.5	0.4
≥20	21	46	0.5	0.7	0.5
Trend, *P*-value			<.001	<.001	<.001
Nonsmokers			0.3		
All smokers					
0	1,151	1,416	1.0	1.0	
1	64	89	0.9	0.9	
2-4	101	202	0.6	0.6	
5-9	169	262	0.8	0.8	
10-19	277	606	0.6	0.7	
≥20	316	682	0.5	0.9	
Trend, *P*-value			<.001	<.001	

[a] Intermittent smokers are those who stopped at least once for 6 mo or more.

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TABLE 5.—*Estimated RR of bladder cancer according to use of filtered and unfiltered cigarettes and currency*

Whether smoking currently	Type of cigarettes	Cases	Controls	Estimated RR[a]	95% CI
Current smokers	Filtered	98	216	1.0	
	Unfiltered	253	320	1.7	1.2–2.4
	Both	793	872	2.0	1.5–2.7
Former smokers	Filtered	45	114	1.0	
	Unfiltered	552	1,104	1.1	0.7–1.6
	Both	319	599	1.0	0.7–1.6
Current or former smokers	Filtered	143	330	1.0[b]	
	Unfiltered	805	1,424	1.5	1.2–1.9
	Both	1,112	1,471	1.6	1.2–2.0

[a] Estimates are adjusted for duration, dose rate, age, sex, and race.
[b] Estimates are also adjusted for currency.

or more before the study had about half the bladder cancer risk of current smokers after accounting for the effects of sex, age, and race. Much, but not all, of the beneficial effect of a longer time since quitting smoking could be attributed to the shorter total duration of smoking. The RRs estimated for the smokers who had quit at least 20 years earlier did not fall to the levels of the nonsmokers. Compared to current continuous smokers, nonsmokers had an RR of 0.4 (0.3–0.4); compared to current intermittent smokers, the nonsmokers' RR was 0.3 (0.2–0.4).

The estimates shown in table 4 were not affected by adjustment for dose rate, filtration, area of residence, or occupational exposure.

Filtered Cigarettes

We compared the 2,229 subjects who exclusively smoked unfiltered cigarettes to the 473 who exclusively smoked filtered cigarettes (table 5). Adjusted for sex, age, race, duration of smoking, dose rate, and whether smoking currently, the RR was estimated as 1.5 (95% CI=1.2–1.9). This apparently greater hazard from unfiltered cigarettes was marked among the current smokers (1.7) and absent among the former smokers (1.1). [The difference in estimated RR was statistically significant (P=.033)]. Subjects who had smoked unfiltered cigarettes and then switched to filtered cigarettes were also at greater risk than those who had only smoked filtered cigarettes (estimated RR=1.6), and the increased risk was restricted to current smokers.

To compare the effects of a year of smoking unfiltered cigarettes and a year of filtered cigarettes and the separate effects of smoking equivalent dose rates of the two types, we estimated logistic regression coefficients for filtered and unfiltered duration and dose rate among all of the current smokers. The estimated increase in bladder cancer risk was 0.6% per year of smoking filtered cigarettes and 1.4% per year of unfiltered cigarettes. The multiplication of risk for each filtered cigarette smoked daily was 1.2 versus 0.8% for each unfiltered cigarette. The greater effect of a year of exposure to unfiltered smoke, compared to filtered smoke, seemed consistent with the overall estimates seen in table 5, but the slightly lesser effect of each additional unfiltered cigarette smoked daily did not. The similarity of the effects of filtered dose rate and unfiltered dose rate is shown in greater detail in table 6. Excluded from table 5 are 85 current smokers (5%) who switched from smoking filtered to unfiltered cigarettes or to smoking both. The estimated RR rose with increasing dose rate for both filtered and unfiltered cigarettes. Subjects who switched from 1–19 unfiltered cigarettes per day to 1–19 filtered ciga-

TABLE 6.—*Estimated RR of bladder cancer, according to use of filtered and unfiltered cigarettes, among current smokers*

Filtered cigarettes/day	Unfiltered cigarettes/day			
	None[a]	1–19	20–39	≥40
None		2.4 (1.3–4.5)	3.1 (1.7–5.6)	3.6 (1.8–6.9)
1–19	1.0	2.4 (1.4–4.1)	2.7 (1.3–5.5)	2.7 (0.8–8.5)
20–39	1.9 (1.1–3.3)	2.1 (1.2–3.7)	3.2 (1.9–5.5)	3.2 (1.5–6.7)
≥40	3.0 (1.4–6.5)	2.9 (1.2–7.0)	3.6 (2.0–6.6)	3.9 (2.1–7.1)
	No. of controls, cases			
None		87,56	172,140	61,57
1–19	102,29	165,122	35,28	8,6
20–39	90,48	100,68	328,321	26,26
≥40	24,21	16,15	71,79	73,85

[a] Reference category is <20 filtered cigarettes per day, never smoked unfiltered. Estimates are adjusted for age, sex, race, and duration of smoking. 95% CIs are shown *in parentheses*.

TABLE 7.—*Estimated fraction of bladder cancer cases attributable to smoking according to age, sex, and race*

Group	Estimated RR	Controls exposed, %	Etiologic fraction
Total group	2.3	62	.44
Males	2.3	70	.48
Females	2.2	38	.32
Males aged 21–44	3.8	62	.63
Males aged 45–64	2.5	74	.53
Males aged 65–84	2.1	69	.42
Females aged 21–44	2.3	50	.40
Females aged 45–64	2.6	50	.44
Females aged 65–84	2.0	30	.24
White	2.2	62	.43
Black	2.6	59	.48
Other race	4.6	55	.64

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rettes per day showed the same RR as those who did not switch (RR=2.4). Similarly, there was little difference for those who had originally smoked 20–39 or 40–99 unfiltered cigarettes.

We observed little or no effect of depth of inhalation among current smokers, former smokers, filter users, nonfilter users, or the total group. The estimated RRs for people who inhaled into the chest and into the throat were 1.1 and 0.9, respectively, compared to those who did not inhale at all.

Etiologic Fraction

We estimated the percentage of bladder cancer associated with smoking among various subpopulations (table 7). About half of the bladder cancer in men and about one-third of the bladder cancer in women was attributable to cigarette smoking. The fractions were somewhat higher among younger people. The fractions were similar among blacks and whites.

DISCUSSION

Many epidemiologic studies conducted during the past 30 years have shown that cigarette smokers face higher risks of developing bladder cancer than do nonsmokers. Previous studies have not been able to analyze in detail the effects of switching to filtered cigarettes because of the close correlations among the variables of interest. These effects can be assessed in this uniquely large case-control study. Because the study population was a representative sample of defined geographic areas accounting for approximately 10% of the U.S. population in 1978, we can also estimate the fraction of bladder cancer caused by cigarette smoking in the United States.

Cessation of smoking clearly reduces the smoker's risk of contracting bladder cancer, as has been reported before (*6–10*). Our data showed that subjects smoking currently have a 50% higher risk than smokers who have quit, even after other characteristics of their smoking histories have been taken into account. Previous reports have also shown that smokers who stopped longer ago have a greater reduction in risk than those who quit recently (*6, 7, 9*). Our data indicate that the beneficial effect of quitting has two biologically distinct components. First, the quitter benefits because he refrains from adding to his total burden of damage. That is, part of the effect of longer time since quitting on reduced RR of bladder cancer is the effect of shorter total duration of exposure. Second, the quitter benefits simply because he has stopped. That is, part of the effect of quitting is not attributable to shorter duration.

Our data suggest that much of the second type of benefit from quitting appears within the 1st year or 2 of stopping. Morrison et al. recently reported a lower risk for former smokers than current smokers and a weak and inconsistent relation between bladder cancer risk and time since quitting among the former smokers, suggesting a rapid decline in risk followed by a plateau (*10*). This pattern appeared in our data among the smokers who had never resumed smoking after having quit for 6 months or more (the majority of smokers). Their rapid decline in RR within 2–4 years and little further decline thereafter could indicate that the increase in risk is quickly halted once the smoker stops. Alternatively, the apparent plateau could reflect some combined effect of earlier starting and earlier stopping. These effects cannot be disentangled for the majority of smokers and have not previously been studied. Analysis of the minority of smokers, those who quit and resumed smoking, does permit adjustment for the effect of age at starting. In our data, this adjustment did slightly lower the estimated RR of the smokers who had quit long ago compared to that of those smoking still. The estimated drop in risk for a specific time since stopping was greater among the intermittent than continuous smokers, but the pattern of decline was similar in the 2 groups. Most of the decline occurred within 5 years of stopping, and risks declined to a plateau above the level of those who never smoked. Lung cancer RRs appear to decline further but more slowly (*15*).

We draw three conclusions from the patterns observed. First, some of the damage done to the bladder by cigarette smoking must be irreversible; otherwise, the risk of quitters eventually would return to the risk of those who never smoked. Second, cigarette smoking probably promotes previously initiated cells to become malignant, since a reduction in RR was apparent within a few years of quitting. Third, the beneficial effect of quitting is not simply a result of age at first exposure, when duration and age are fixed. In short, it seems likely that cigarette smoke contains both initiators and promoters for bladder carcinogenesis. [Such a combined effect would be consistent with experimental data showing that tobacco smoke contains compounds that initiate and promote tumors of the skin and other sites (*16*)].

Our data on the types of cigarettes smoked showed that unfiltered cigarettes produced greater bladder cancer risks than filtered cigarettes did. Switching from unfiltered to filtered did not lower risk very much, if dose rate remained the same. Why switching did not measurably lower bladder cancer risk remains unclear. It is possible that imprecision in our data obscured a real reduction. The effect of filtered cigarettes would not be readily apparent if subjects were classified only according to their current habits, since the majority of older people currently smoking filtered cigarettes once smoked unfiltered cigarettes.

Two provocative findings in our data were the reduced effects of filtration and dose rate among the former smokers. Perhaps dose rate and filtration measure elements of the exposure to cigarettes that are partly reversible, whereas total duration measures mostly irreversible damage to the bladder.

Although bladder cancer is hardly the most common danger associated with cigarette smoking, it is an important risk that the typical smoker in the United States faces. In addition, because cigarette smoking has been so prevalent in the United States in past decades, it accounts for a major portion of bladder cancer. In our

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estimation, half of the bladder cancers among men and one-third of those among women can be attributed to smoking.

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